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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/330,903	06/11/99	GONDA I	6513/061US1

EXAMINER	
SCHNIZER, R	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/330,903	GONDA ET AL.	
	Examiner	Art Unit	
	Richard Schnizer	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 June 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-56* is/are pending in the application.

4a) Of the above claim(s) *46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-45 and 47-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/25/01 has been entered.

A preliminary amendment was received and entered as Paper No. 16 on 6/25/01. Claims 1-20 were canceled and claims 21-56 were added as requested. Newly submitted claim 46 is directed to an invention that is independent or distinct from the invention originally claimed because it is unrelated to that invention. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions have different modes of operation and different effects. For example, the invention of claims 21-45, 47-56 does not require or result in the isolation of cells, however this is the intended outcome of the invention of claim 46.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the

merits. Accordingly, claim 46 is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 112 as follows:

> The second application (which is called a continuing application) must be an application for a patent for an invention which is also disclosed in the first application (the parent or provisional application); the disclosure of the invention in the parent application and in the continuing application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *In re Ahlbrecht*, 168 USPQ 293 (CCPA 1971).

This Application claims priority to application number 08/752,946, filed 11/21/96, now US Patent 5,906,202, issued 5/25/99. However, instant claims 21-56 recite the limitation of "a condensed polynucleotide", and there is no support for this limitation in US Patent 5,906,202. Furthermore, '202 provides no support for the following claim limitations, a lipid-based carrier (instant claims 23-25, 37, 38, and 40); a nucleotide sequence encoding CFTR, a ribozyme, an oligonucleotide, an antisense polynucleotide, or any condensing agent (instant claims 30-36, 39); or methods of delivering recombinant viral envelope proteins (instant claims 47 and 48). For these reasons, the priority date for the instant claims is considered to be that of provisional application 60/089,146 which is 6/12/98.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claim 52 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 51. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). The only difference between these two claims is the inclusion in claim 52 of the word "of", after the word "diameter". This provides no meaningful distinction between the two claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-27, 48, 51-53, and 55 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 21-27 are drawn to methods for administering a condensed polynucleotide by inhalation. These claims require determination of a patient's "total respiratory tract capacity", and "inhaling an additional measured amount of particle-free air wherein the additional volume is related to the volume of the patient's anatomical dead space." The specification fails to provide literal support for determining the total respiratory tract capacity of a patient, or for relating any volume of air to a patient's anatomical dead space, thus these method steps represent new matter.

Claim 36 recites an aerosol composition comprising particles having a polynucleotide to protamine sulfate weight ratio of from about 2:1 to about 11:1. The specification fails to provide literal support for this range, thus it represents new matter.

Claims 48, 51, and 52 recite particles having a diameter of from 1-8 nm, and claims 53 and 55 recite particles with a size range of about 0.5-12 microns. Additionally, claim 53 recites pore sizes from about 0.5 to about 6 microns. The specification provides no literal support for these precise size ranges, thus they represent new matter.

It is further noted that the citations provided at pages 6 and 7 of Applicant's response filed 6/25/01 do not provide support for the limitations discussed above.

For these reasons, one of skill in the art could not conclude that Applicant was in possession of the claimed invention at the time of filing.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21-27, 33, and 40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 21-27 are indefinite because it is unclear how the measured volume of particle free air must be related to the total respiratory tract volume or to a region of lung targeted for treatment. These parameters can all be expressed as numerical values and can therefore be related simply by their magnitudes. It is unclear what relationship is required by the claims. Similarly it is unclear how the volume of aerosol-comprising particles in step (c) should be related to a region of the respiratory tract, and how the volume of particle-free air in step (d) should be related to the volume of the patient's anatomical dead space.

Claims 21-27 are also indefinite because it is unclear what is intended by the phrase "total respiratory tract capacity". The specification implies that the respiratory tract begins in an area which includes the oropharyngeal region and the trachea. See page 14, lines 11-14. Does this

area exclude the mouth and nasal passages? It is unclear what structures are considered by Applicant to constitute the total respiratory tract, so it is unclear to what capacity the claims refer.

Claim 27 is indefinite because it is unclear what is intended by the limitation "so as to approximately fill the peripheral region". When is a region "approximately" filled? One of skill in the art cannot know what volumes are encompassed by the claims and which are not. Furthermore, the term "region" is confusing because it is defined by the specification at page 14 as meaning an area of the respiratory tract "which is based on an approximate model of the lung." However, the specification does not set forth any approximate model of the lung which defines such regions as the peripheral region, the central regions, or the upper region of the anatomical dead space, in sufficient detail to allow one of skill in the art to clearly understand the metes and bounds of the claims.

Claim 33 recites "the antisense polynucleotide" without proper antecedent basis. Substitution of the word "oligonucleotide" for the word "polynucleotide" is suggested.

Claim 40 is ungrammatical. Insertion of the word "comprises" between the words "carrier" and "an" is suggested.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

Claims 41-43, 45 and 49-52 are rejected under 35 U.S.C. 102(e) as being anticipated by Debs (US Patent 5,756,353, issued 5/26/98), as evidenced by Crook et al (Gene Therapy 3(9): 834-839, 9/1996).

Debs teaches delivery to the lungs of an individual an aerosol comprising a double stranded polynucleotide, and expression of the polynucleotide in transfected cells of the lungs in the individual. See column 15, lines 26-43. The size of the aerosol particles can be adjusted based on the intended delivery site within the respiratory tract. A size range of from 0.5-5 microns is taught for targeting alveoli, and a size range of 5-10 microns is taught for airway delivery. These ranges overlap, or are encompassed by, the claimed size ranges. See column 12, lines 51-56, 60, and 61; and claims 1, and 14-16. The polynucleotides of Debs can be considered to be condensed because they are complexed with cationic liposomes, such as DOTAP, in such a way as to bind to the surface of the liposomes, or to be entrapped within the liposomes. See column 5, lines 28-36, and column 10, lines 53-59. These structures would be expected to decrease the volume of space occupied by the nucleic acid, and would satisfy the definition of a condensed nucleic acid found at page 10 of the specification. This is supported by Crook who teaches that DOTAP-encapsulated plasmid DNA is considered to be condensed. See abstract.

Thus Debs anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 21-24, 27-29, 37, 38, 47, and 53-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Debs in view of Crook et al (Gene Therapy 3(9): 834-839, 9/1996) and Schuster et al (US Patent 5,906,202, issued 5/25/99).

Debs teaches a method of delivering by inhalation DNA condensed with cationic lipids. The lipid may be DOTAP. See claim 3, column 15. Debs does not teach determining a patient's total respiratory tract capacity, inhaling a measured volume of particle-free air, or inhaling an additional measured volume of particle-free air. Debs also does not teach a disposable package for use in aerosolized delivery of drugs to the lungs, or a drug delivery device comprising a channel with an opening through which air can be inhaled.

Crook teaches that DOTAP-encapsulated plasmid DNA is considered to be condensed. See abstract.

Schuster teaches a device and method of delivering a volume of aerosol to a target area of a lung. The method comprises measuring a volume of particle-free air inhaled into the lungs, drawing a measured volume of aerosol into the respiratory tract, and inhaling additional particle-free air, insufficient to fill the upper region of the patient's respiratory tract. See claim 6, bridging

columns 38 and 39. The device comprises a channel with a first opening in to which air can be inhaled, a second opening from which a patient can withdraw air, and a third opening through which aerosolized particles enter the channel. See Fig. 4, and column 15, line 45 to column 16, line 17. Schuster teaches the delivery of gene vectors by this method. See column 2, line 33; paragraph bridging columns 30 and 31, and claims 11-13. Schuster does not explicitly recite measuring the total respiratory tract capacity of an individual, but this limitation is implicit in claims 4 and 6 which require knowledge of the patient's total respiratory tract volume. See columns 38 and 39. Schuster also teaches disposable packages for delivery of aerosolized drugs to the lungs. The packages comprise a collapsible wall against which a force may be applied in order to move through porous membrane a flowable liquid comprising the drug. The pores may be from 0.25 to 6 microns, and the particles generated may be from about 0.5 to about 12 microns. See claim 1, column 38; and column 12, lines 2-12; column 14, lines 1-30; and claim 12, column 34.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the delivery device and method of Schuster in the method of Debs. One would have been motivated to do so because Debs teaches that the choice of a nebulizer system will vary with the choice of target site (see column 12, lines 37-47) and Schuster teaches a single device and method which allow efficient targeting of the aerosol particles to desired areas of the lung. See column 2, lines 4-9.

The device of Schuster results in particles of from about 0.5 to about 12 microns, encompassing the claimed range of about 1-8 microns (claims 45 and 51), and comprises membrane pores ranging from 0.25 to 6 microns, which overlaps the claimed range of 0.5 to about 25 microns (claims 28, 29, 37, 38, 47, and 53-56). In cases where a claimed range overlaps or lies inside a range disclosed by the prior art, a *prima facie* case of obviousness exists. See MPEP 2144.05(I). Furthermore, the size range of the particles can be considered to be a result-effective variable. That is, the results of the method are effected by the size of the particles, and one of ordinary skill would be motivated to optimize the size range of the particles in order to achieve the best results. Generally, differences in the range of sizes will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating that this concentration is critical. See MPEP 2144.05(II) (A) and (B). In this case, the there is no evidence to suggest that the range of 1-8 microns will have a different effect than the range of 0.5 to 12 microns. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454 105 USPQ 233, 235 (CCPA 1955).

Thus the invention as a whole was prima facie obvious.

Claims 21-25, 27-29, 37, 40-43, 45, 47, 48, 49-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yonemitsu et al (Gene Therapy 4(7): 631-638, 7/1997) in view of Crook

et al (Gene Therapy 3(9): 834-839, 9/1996) and Schuster et al (US Patent 5,906,202, issued 5/25/99).

Yonemitsu teaches a method of transferring polynucleotides into airway epithelium in which cationic liposomes are fused with Sendai virus to make artificial viral envelopes. The nucleic acids of Yonemitsu can be considered to be condensed because they are complexed with cationic liposomes. The complexes are delivered as an aerosol. See entire document, especially abstract. Yonemitsu does not teach determining a patient's total respiratory tract capacity, inhaling a measured volume of particle-free air, or inhaling an additional measured volume of particle-free air. Yonemitsu also does not teach a disposable package for use in aerosolized delivery of drugs to the lungs, or a drug delivery device comprising a channel with an opening through which air can be inhaled.

Crook teaches that cationic liposome-encapsulated plasmid DNA is condensed. See abstract.

Schuster teaches a device and method of delivering a volume of aerosol to a target area of a lung. The method comprises measuring a volume of particle-free air inhaled into the lungs, drawing a measured volume of aerosol into the respiratory tract, and inhaling additional particle-free air, insufficient to fill the upper region of the patient's respiratory tract. See claim 6, bridging columns 38 and 39. The device comprises a channel with a first opening in to which air can be inhaled, a second opening from which a patient can withdraw air, and a third opening through which aerosolized particles enter the channel. See Fig. 4, and column 15, line 45 to column 16,

line 17. Schuster teaches the delivery of gene vectors by this method. See column 2, line 33; paragraph bridging columns 30 and 31, and claims 11-13. Schuster does not explicitly recite measuring the total respiratory tract capacity of an individual, but this limitation is implicit in claims 4 and 6 which require knowledge of the patient's total respiratory tract volume. See columns 38 and 39. Schuster also teaches disposable packages for delivery of aerosolized drugs to the lungs. The packages comprise a collapsible wall against which a force may be applied in order to move through porous membrane a flowable liquid comprising the drug. The pores may be from 0.25 to 6 microns, and the particles generated may be from about 0.5 to about 12 microns. See claim 1, column 38; and column 12, lines 2-12; column 14, lines 1-30; and claim 12, column 34.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the delivery device and method of Schuster in the method of Yonemitsu. One would have been motivated to do so because Schuster teaches a device and method which allow efficient targeting of the aerosol particles to desired areas of the respiratory tract, and that targeting of gene vectors to specific areas may be desirable. See column 2, lines 4-9; and paragraph bridging columns 4 and column 5. Further, the device of Schuster is convenient because it is pocket-sized, hand-held, it allows controlled release of measured volumes for enhanced repeatability, and it record the precise date, time, and amount of aerosol released for each administration. See column 5, lines 5-14. The previous rejection discussed the obviousness of claimed ranges when the prior art teaches ranges which overlap or encompass the claimed ranges. This discussion, relevant to

the Schuster references, applies to claims 28, 29, 37, 40-43, 45, 47, 48, and 49-56 of this rejection.

Thus the invention as a whole was prima facie obvious.

Claims 21, 22, 26-29, 34-36, 41-45, and 49-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carson et al (US Patent 5,849,719, issued 12/15/98)), Gagne et al (Proc. Int. Symp. Controlled Release Bioact. Mater. 24: 641-642, 1997), and Schuster et al (US Patent 5,906,202, issued 5/25/99).

Carson teaches a method of inducing an immune response in a host comprising delivering to mucosal cells an aerosolized polynucleotide encoding an immunogenic polypeptide, wherein the immunogen is expressed. The mucosal cells may be in the lungs. See column 4, lines 48-57; and column 22, claims 1-3. The polynucleotide should be naked but may be associated with absorption promoters. See column 11, lines 5-12; and column 12, lines 47-51. Carson does not teach determining a patient's total respiratory tract capacity, inhaling a measured volume of particle-free air, inhaling an additional measured volume of particle-free air, or a condensed polynucleotide. Carson also does not teach a disposable package for use in aerosolized delivery of drugs to the lungs, or a drug delivery device comprising a channel with an opening through which air can be inhaled.

Schuster teaches a device and method of delivering a volume of aerosol to a target area of a lung. The method comprises measuring a volume of particle-free air inhaled into the lungs,

drawing a measured volume of aerosol into the respiratory tract, and inhaling additional particle-free air, insufficient to fill the upper region of the patient's respiratory tract. See claim 6, bridging columns 38 and 39. The device comprises a channel with a first opening in to which air can be inhaled, a second opening from which a patient can withdraw air, and a third opening through which aerosolized particles enter the channel. See Fig. 4, and column 15, line 45 to column 16, line 17. Schuster teaches the delivery of gene vectors by this method. See column 2, line 33; paragraph bridging columns 30 and 31, and claims 11-13. Schuster does not explicitly recite measuring the total respiratory tract capacity of an individual, but this limitation is implicit in claims 4 and 6 which require knowledge of the patient's total respiratory tract volume. See columns 38 and 39. Schuster also teaches disposable packages for delivery of aerosolized drugs to the lungs. The packages comprise a collapsible wall against which a force may be applied in order to move through porous membrane a flowable liquid comprising the drug. The pores may be from 0.25 to 6 microns, and the particles generated may be from about 0.5 to about 12 microns. See claim 1, column 38; and column 12, lines 2-12; column 14, lines 1-30; and claim 12, column 34.

Gagne teaches that association of plasmid DNA with protamine sulfate protects it from degradation during aerosolization. See page 641, column 2, lines 4-8 of paragraph 5.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the device and method of Schuster in the method of Carson. One would have been motivated to do so because the method and device of Schuster allow efficient targeting of the

aerosol particles to desired areas of the respiratory tract, and that targeting of gene vectors to specific areas may be desirable. See column 2, lines 4-9; and paragraph bridging columns 4 and column 5. Further, the device of Schuster is convenient because it is pocket-sized, hand-held, it allows controlled release of measured volumes for enhanced repeatability, and it record the precise date, time, and amount of aerosol released for each administration. See column 5, lines 5-14.

One would have been motivated to condense the DNA of Carson with the condensing agent of Gagne because Gagne teaches that this stabilizes the DNA against aerosolization-induced degradation.

The previous rejection discussed the obviousness of claimed ranges when the prior art teaches ranges which overlap or encompass the claimed ranges. This discussion, relevant to the Schuster references, applies to claims 28, 29, 34-36, 41-45, and 49-56 of this rejection.

Thus the invention as a whole was *prima facie* obvious.

Claims 28, 29, 37, 38, 47, and 53-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Debs (US Patent 5,756,353, issued 5/26/98), in view of Crook et al (Gene Therapy 3(9): 834-839, 9/1996) and Lloyd et al (US Patent 5,497,763, issued 3/12/96).

Debs teaches delivery to the lungs of an individual an aerosol comprising a double stranded polynucleotide, and expression of the polynucleotide in transfected cells of the lungs in the individual. See column 15, lines 26-43. The size of the aerosol particles can be adjusted based on

the intended delivery site within the respiratory tract. A size range of from 0.5-5 microns is taught for targeting alveoli, and a size range of 5-10 microns is taught for airway delivery. These ranges overlap, or are encompassed by, the claimed size ranges. See column 12, lines 51-56, 60, and 61; and claims 1, and 14-16. The polynucleotides of Debs can be considered to be condensed because they are complexed with cationic liposomes, such as DOTAP, in such a way as to bind to the surface of the liposomes, or to be entrapped within the liposomes. See column 5, lines 28-36, and column 10, lines 53-59. These structures would be expected to decrease the volume of space occupied by the nucleic acid, and would satisfy the definition of a condensed nucleic acid found at page 10 of the specification. This is supported by Crook who teaches that DOTAP-encapsulated plasmid DNA is considered to be condensed. See abstract. Debs also teaches that the aerosol may be generated and delivered by a nebulizer. See column 12, lines 25-36.

Debs does not teach a member comprising pores having an exit diameter of 0.5 to 25 microns, a disposable package for delivery of aerosolized drugs to the lungs, or a drug delivery device having a channel with a first opening in to which air can be inhaled, a second opening from which a patient can withdraw air, and a third opening through which aerosolized particles enter the channel.

Lloyd teaches disposable packages for delivery of aerosolized drugs to the lungs. The packages comprise a collapsible wall against which a force may be applied in order to move through porous membrane a flowable liquid comprising the drug. The pores may be from 0.5 to 6 microns, and the particles generated may be from about 0.5 to about 12 microns. See claim 1,

column 33; and claim 12, column 34. Lloyd also teaches a drug delivery device comprising a channel with a first opening in to which air can be inhaled, a second opening from which a patient can withdraw air, and a third opening through which aerosolized particles enter the channel. See abstract; Fig. 9; and column 22, lines 28-40.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the packages and delivery device of Lloyd in the method of Debs in order to deliver polynucleotides to the respiratory tract. One would have been motivated to do so because Lloyd teaches that nebulizers suffer from many disadvantages such as being large in size and not hand-held, and producing a poorly controlled distribution of particle sizes. See column 3, lines 36-67. The invention of Lloyd is designed to improve on the performance of nebulizers, thus one of skill in the art would be motivated to use it in the method of Debs.

Thus the invention as a whole was *prima facie* obvious.

Claim 30 is rejected under 35 U.S.C. 103(a) as being unpatentable over Debs, Crook, and Lloyd as applied to claims 28, 29, 37, 38, 47, and 53-56 above, and further in view of McClachlan et al (Gene Therapy 3(12): 1113-1123, 12/1996)).

Debs and Crook can be combined with Lloyd to render obvious a method of generating an aerosol containing a condensed polynucleotide by combining a polynucleotide with a condensing agent and forcing the condensed polynucleotide through a member comprising exit porous having a diameter from 0.5 to 25 microns.

These references do not teach a nucleic acid construct encoding a cystic fibrosis transmembrane conductance regulator (CFTR).

McClachlan teaches a plasmid encoding CFTR, and a method of delivering a complex of the plasmid and DOTAP to the trachea to study gene function and gene delivery in the process of developing potential treatments for cystic fibrosis (CF). See abstract.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the plasmid/complex of McClachlan in the method of Debs as modified by Lloyd. One would have been motivated to do so because Debs suggests the possibility of treating CF by administration of CFTR nucleic acids, because McClachlan suggests studying the function of CFTR and the process of its delivery to the trachea, and because the method of Lloyd improves on the nebulizer-mediated delivery of Debs.

Thus the invention as a whole was *prima facie* obvious.

Claims 28, 31, 32, 37-39, 41, 45, and 47-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Collins (US Patent 5,736,327, issued 4/7/98) in view of Lloyd et al (US Patent 5,994,315, issued 11/30/99).

Collins teaches an aerosol composition comprising either an antisense oligonucleotide or a ribozyme. The oligonucleotide or ribozyme may be complexed with liposomes (DOTMA or DOTAP) and polycations (condensing agents), and polynucleotides may be delivered to the bronchi.. See column 13, lines 52 and 53; column 14, lines 7-14, 25-29, 48, and 49, and column

15, lines 55-57. Collins does not teach a method of making an aerosol by forcing a condensed polynucleotide against a member comprising pores having an exit diameter of 0.5 to 25 microns.

Lloyd teaches a method and a device for making aerosols and delivering them to the lungs. The device uses disposable packages comprising a collapsible wall against which a force may be applied in order to move through porous membrane a flowable liquid comprising the drug. The pores may be from 0.5 to 6 microns, and the particles generated may be from about 0.5 to about 12 microns. See claim 1, column 33; and claim 12, column 34.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the packages and delivery device of Lloyd in order to produce the aerosol composition of Collins. One would have been motivated to do so because Collins suggests that the aerosols should be delivered bronchially, and the device of Lloyd is designed to target specific regions of the respiratory tract, including the bronchial tubes. See column 26, lines 12-15.

Thus the invention as a whole was *prima facie* obvious.

Claims 28, 32, 33, 37-39, 41, 45, and 47-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nyce et al (US Patent 5,994,315, issued 11/30/99) in view of Crook et al (Gene Therapy 3(9): 834-839, 9/1996) and Lloyd et al (US Patent 5,994,315, issued 11/30/99).

Nyce teaches an aerosol composition comprising antisense oligonucleotides complexed with cationic lipids (DOTAP), and a method of making the composition using a nebulizer. The antisense oligonucleotide may be targeted against elastase. See claim 40, column 34; column 5,

lines 37-40; column 6, lines 32-39; column 12, lines 16-21; and column 13, lines 22 and 23 (SEQ ID NO: 31). Nyce does not teach a method of making an aerosol by forcing a condensed polynucleotide against a member comprising pores having an exit diameter of 0.5 to 25 microns.

Crook teaches that DOTAP-encapsulated DNA is condensed. See abstract.

Lloyd teaches a device for making aerosols and delivering them to the lungs. The device uses disposable packages comprising a collapsible wall against which a force may be applied in order to move through porous membrane a flowable liquid comprising the drug. The pores may be from 0.5 to 6 microns, and the particles generated may be from about 0.5 to about 12 microns. See claim 1, column 33; and claim 12, column 34.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the packages and delivery device of Lloyd in the method of Nyce in order to deliver condensed antisense oligonucleotides to the respiratory tract. One would have been motivated to do so because Lloyd teaches that nebulizers suffer from many disadvantages such as being large in size and not hand-held, and producing a poorly controlled distribution of particle sizes. See column 3, lines 36-67. The invention of Lloyd is designed to improve on the performance of nebulizers, thus one of skill in the art would be motivated to use it in the method of Nyce.

Thus the invention as a whole was *prima facie* obvious.

Claims 34-36, and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Debs, Crook, and Lloyd as applied to claims 28, 29, 37, 38, 47, and 53-56 above, and further in view of Gao et al (US Patent 5,795,587, issued 8/18/98) .

Debs and Crook can be combined with Lloyd to render obvious a method of generating an aerosol containing a condensed polynucleotide by combining a polynucleotide with a condensing agent and forcing the condensed polynucleotide through a member comprising exit porous having a diameter from 0.5 to 25 microns.

These references do not teach a polynucleotide condensed with protamine sulfate or polylysine.

Gao teaches stable lipid-comprising nucleic acid delivery particles in which the nucleic acid is complexed with either polylysine or protamine. The amount of polycation may range from 0.1 microgram to 10 micrograms per microgram of nucleic acid. See column 9, line 40 to column 10 line 11, especially column 10, lines 6-11. See also claims 4 and 11. The particles may be delivered as an aerosol. See column 11, lines 30-34. With respect to instant claim 39, Gao teaches that oligonucleotides may be delivered as complexes with polycations and lipids. See column 3, lines 8-10.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use protamine sulfate or polylysine to condense the DNA of Debs prior to formation of an aerosol, as taught by Gao. One would have been motivated to do so because the lipid/nucleic acid/polycation complexes of Gao are highly concentrated and are stable and retain biological

activity for prolonged periods of time. See abstract, and column 3, lines 40-45. The range of polynucleotide to polycation ratios taught by Gao (10:1 to 1:10) overlaps the claimed range (2:1 to 1:11). In cases where a claimed range overlaps a range disclosed by the prior art, a *prima facie* case of obviousness exists. See MPEP 2144.05(I). "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454 105 USPQ 233, 235 (CCPA 1955).

In further consideration of claim 38, it is also noted that Gao teaches the use of DC-Chol in the formation of the complexes. See column 8, lines 7 and 8.

Thus the invention as a whole was prima facie obvious.

Thus the invention as a whole was *prima facie* obvious.

Claim 44 is rejected under 35 U.S.C. 103(a) as being unpatentable over Debs (US Patent 5,756,353, issued 5/26/98) in view of Crook et al (Gene Therapy 3(9): 834-839, 9/1996), Carson et al (US Patent 5,849,719, issued 12/15/98), and Mitchell et al (Immunotechnology 1(3-4): 211-219, 12/1995).

Debs teaches delivery to the respiratory tract of an individual an aerosol comprising a double stranded polynucleotide, and expression of the polynucleotide in transfected lung cells of the individual. See column 15, lines 26-43; Fig. 2; and claims 1 and 12. The polynucleotides of Debs can be considered to be condensed because they are complexed with cationic liposomes, such as DOTAP, in such a way as to bind to the surface of the liposomes, or to be entrapped

within the liposomes. See column 5, lines 28-36, and column 10, lines 53-59. These structures would be expected to decrease the volume of space occupied by the nucleic acid, and would satisfy the definition of a condensed nucleic acid found at page 10 of the specification. This is supported by Crook who teaches that DOTAP-encapsulated plasmid DNA is considered to be condensed. See abstract. Debs is silent as to whether an immune response was raised against the expressed polypeptide.

Carson teaches a method of inducing an immune response in a host comprising delivering to mucosal cells an aerosolized polynucleotide encoding an immunogenic polypeptide, wherein the immunogen is expressed. The mucosal cells may be in the lungs. See column 4, lines 48-57; and column 22, claims 1-3.

Mitchell et al teach the induction of anti-HIV antibodies by transfection of lung epithelium by lavage with plasmid DNA condensed by lipospermine. Expression of HIV antigen in lung cells was inferred by the presence of anti HIV-antibodies in lung tissue at the site of transfection. See abstract; page 212, column 2, lines 12-17 of first full paragraph; page 213, column 2, first full paragraph; page 215, paragraph bridging columns 1 and 2, especially column 2, lines 7-12; Fig. 2 on page 216; and Fig. 3 on page 217.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the method of Debs to deliver a condensed polynucleotide encoding an immunogenic polypeptide to the lungs because Carson teaches that one can invoke an immune response by delivery of nucleic acids to lung cells. Even though Carson suggests the delivery of naked

polynucleotides, one would have been motivated to use condensed polynucleotides with a reasonable expectation of success because Mitchell teaches that condensed polynucleotides delivered to lung cells can be expressed there and can induce a mucosal immune response, and because Debs teaches that aerosolized nucleic acid/cationic liposome complexes were competent to transfect lung cells and to produce an encoded protein.

Thus the invention as a whole was *prima facie* obvious.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 103-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is usually in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached at 703-305-6608. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Patsy Zimmerman whose telephone number is 703-308-8338.

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PRIMARY EXAMINER
GROUP ~~1800~~ / 1630